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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/786,907	BOGEN ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37,77,83-108 and 118-126* is/are pending in the application.

4a) Of the above claim(s) *1-37,77,84-87,93,94,97 and 101-108* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *83, 88-92, 95, 96, 98-100 and 118-126* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/22/08 has been entered.

2. Claims 1-37, 77, 83-108, and 118-126 are all the pending claims for this application.

3. Claims 1-37, 77, 84-87, 93, 94, 97, 101-108 are withdrawn from examination.

4. Claims 83, 88, 95, 96, 98, and 99 were amended and Claims 109-117 cancelled in the Response of 1/22/08.

5. Claims 83, 88-92, 95, 96, 98-100 and 118-126 are all the pending claims under examination with targeting units for a ligand species of soluble CD40 ligand and the chemokines, RANTES and MIP-1α, and the species of antigenic units for an antigenic scFv.

Withdrawal of Objections

Specification

6. The objection to the figure legends for Figures 8-11 for disclosing the linker sequences, $(GlyGlyGlySerSer)_3$ (Figures 8 and 9) and $(GlyGlyGlyGlySer)_3$ (Figures 10 and 11) with out reference to a SEQ ID NO is withdrawn.

The amendments to the specification for the figure legends on pp. 2-4 of the Response of 1/22/08, overcome the objection.

Claim Objections

7. The objection to Claims 109 and 112 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is moot in view of the cancelled claims.

8. The objection to Claims 83 and 112 for inconsistent spelling of "disulfide" and "disulphide" is moot in view of cancelled Claim 112.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, second paragraph

9. The rejection of Claims 83, 88-92, 95, 96, 98-100 and 109-126 in lacking antecedent basis for the recitation "said monomer units" in Claim 83 is moot for cancelled Claims 109-117 and withdrawn for Claims 83, 88-92, 95, 96, 98-100 and 118-126 in view of the amendment of Claim 83 to recite "said monomer unit".

10. The rejection of Claims 83, 88-92, 95, 96, 98-100, 109, and 111-126 for the recitation "comprising a hinge region" in Claim 83 is moot for cancelled Claims 109 and 111-117. The rejection is withdrawn for Claims 83, 88-92, 95, 96, 98-100 and 118-126 in view of the amendment of Claim 83 to recite "Ig hinge."

Applicants' comments on pp. 26-27 of the Response of 1/22/08 are acknowledged.

11. The rejection of Claims 88-92, 95, 96 and 98 in lacking antecedent basis for the recition "targeting units" in Claims 88, 95, 96 and 98 is withdrawn in view of the amendment of Claims 88, 95, 96 and 98 to recite "said targeting unit."

12. The rejection of Claims 99 and 100 in lacking antecedent basis for the recitation "antigenic units" in Claim 99 is withdrawn in view of the amendment of Claim 99 to recite "said antigenic unit."

13. The rejection of Claim 109 for the broadening recitation "wherein said dimerization motif comprises…an immunoglobulin domain" is moot for the cancelled claim.

14. The rejection of Claim 111 for the broadening recitation "where the hinge region has the ability to form one or several covalent bonds" is moot for the cancelled claim.

Enablement (1)

15. The rejection of Claims 118, 121, 122 and 124-126 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement as set forth in the Office Action of 7/19/07 is withdrawn.

In the Office Action of 7/19/07, the Examiner stated:

"The specification does not disclose a cistronic vector encoding both monomeric units that are expressed in equimolar amounts and that would allow the expressed monomeric subunits to dimerize into a dimeric antibody in vivo. The specification teaches each monomeric unit being encoded by a vector. The specification does not disclose a) administering separate nucleic acid vectors encoding each of the monomer units to a patient for inducing production of the dimeric antibody (Claim 118) or b) pharmaceutical compositions comprising vectors encoding a nucleic acid encoding each of a monomer unit (Claim 121) or host cells comprising vectors encoding a nucleic acid encoding each of a monomer unit (Claim 122) where the intended use is to induce a *protective* immune response against cancer such as myeloma or lymphoma in a patient or c) vaccines comprising a nucleic acid for each of a monomeric unit and the success in obtaining a fully assembled dimeric antibody that could treat or prevent cancer such as myeloma or lymphoma in a patient (Claims 124-126). The art known meaning of a vaccine is that it provides a prophylactic effect (see attached copy of Stedman's Medical Dictionary definition for "vaccine"). Thus the specification does not demonstrate with a sufficient number of working examples that the pharmaceutical compositions comprising a nucleic acid encoding a monomer unit much (of Claim 83) much less two or more nucleic acids each encoding a different monomer unit, could reasonably produce a therapeutic gene immunization effect in vivo much less in a human. Further, the specification provides no example of the vaccine compositions comprising a nucleic acid encoding a monomer unit (of Claim 83) much less that two or more nucleic acids each encoding a different monomer unit, could reasonably produce a prophylactic gene immunization effect in vivo much less in a human.

State of the Art for Gene Immunization

The Examiner incorporates the references cited by Applicants in the Response of 5/7/07 as providing the background and state of art for gene immunization protocols. Thus based on the foregoing discussion distinguishing of the Felgner reference, one skilled in the art would not be reasonably apprised from the specification or the prior art how to use the instant claimed pharmaceutical and vaccine compositions. Further to practice using the pharmaceutical and vaccine compositions for the instant nucleic acid, one of skill in the art would be required to perform undue trial and error experimentation to determine how to express equimolar amounts of the nucleic acid encoding a monomer unit in order to be reasonably assured that two monomer units could dimerized into a dimeric antibody. For all of these reasons, the claims are not enabled as of the application filing date."

Applicants' allegations on pp. 28-32 of the Response of 1/22/08 have been considered and are found persuasive. Applicants' admission on the record is that the "dimmers" ["dimers"] in the present application are formed from homodimers, which assemble spontaneously from the expression products of one single vector (due to the

presence of the dimerization unit in the monomers). It should be noted that only expression of one vector is necessary in order for the claimed embodiments to work."

Claim Rejections - 35 USC § 102.

16. The rejection of Claims 83, 88-92, 96, 98, 109-117, 119, 120 and 123 are rejected under 35 U.S.C. 102(e) as being anticipated by Herman (US 20050069549; published March 31, 2005; filed Jan 14, 2003) is withdrawn.

The rejection is moot for cancelled Claims 109-117. The rejection is withdrawn for Claims 83, 88-92, 96, 98, 119, 120 and 123 in view of the amendment of Claim 83 to recite the spatial relationship of the elements of the nucleic acid construct over the elements of Herman.

The Examiner submits that the closest embodiment that Herman teaches and which is now considered distinguishable from the pending claims is the following:

[0345] "One or both components (they may be the same or different) may be a dAb, a scFv, an Fab, a minibody moiety or a substantially intact antibody, for example both may be scFvs and the resulting product may be a diabody, triabody, or tetrabody. For example in a preferred embodiment the bispecific antibody comprises two dAb components comprising linked via a linker (see above) and having at least at least part of a constant region for fusion for example to a toxin (eg. at least a partial hinge region, and preferably also at least a partial CH2 domain (optionally also at least a partial CH3 domain)."

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement (2)

17. The rejection of Claims 118, 121, 122 and 124-126 are rejected under 35 U.S.C. 112, first paragraph, for lack of enablement is maintained for reasons of record as set forth in the Office Actions of 11/7/06 and 7/19/07.

In the Office Action of 7/19/07, the Examiner stated that the specification is not enabling for the full scope of the claims because:

> "The specification does not teach gene immunization (or gene therapy) methods for treating or *preventing* a cancer much less a myeloma or lymphoma or inducing a *prophylactic* T- or B-cell immune response in a *human patient* with a *nucleic acid* of the claims examined in the Office Action of 11/7/06, the vector comprising the nucleic acid or a vector-transfected cell or cell line encoding the recombinant antibody-based molecule. There are no working examples in Applicant's specification to guide the skilled artisan in practicing the administration of the nucleic acid, vector or transfected host cell, more especially by injection and electroporation, which results in *a) induction of an immune B- and T cell response or b) a reduction in a cancer such as myeloma or lymphoma*. The goal of tumor vaccination is the induction of tumor immunity to *prevent* tumor occurrence or recurrence and Applicants have not demonstrated any such effect(s) with the nucleic acid as originally examined."

a) Applicants' allegations on pp. 18-24 of the Response of 1/22/08 and copies of the cited references (Stevenson (2004); Eisen (1968); Schulenburg (1971); Eisen (1985); Brunsvik [*actually Fredriksen (Examiner's correction)*] (2007); Schjetne (2007); and Fredriksen (2006)) have been considered and are not found persuasive.

Applicants allege the claims are fully enabled for the scope of Vaccibody embodiments because: expression product for specific Vaccibody protein to idiotypic Fv

from the murine MOPC315.4 tumor (i.e., the antigenic unit is an idiotype derived from the murine multiple myeloma MOPC315.4 cell line) was detected in sera of mice (Example 5 on pp. 34-35 of the specification); methods for using the pharmaceutical compositions to treat and prevent myeloma showing intra-muscular injection and electroporation for expression in vivo (p. 28 of the specification and Examples 5 and 6; citing Stevenson (2004) as support for established route of injection); the murine MOPC315.4 multiple myeloma animal model is correlative and predictive for treatment and prevention of multiple myeloma in other animals (citing Eisen (1968), Schulenburg (1971) and Eisen (1985)); the term "vaccine connotes prevention and/or diminishment of a disease in comparison to no vaccine at all"; the specification describes procedures for administering Vaccibody to produce a protective effect and the generation of a protective effect against development of tumors (Figures 21a and 21b; 22 and 23); and further evidence of prophylactic and preventative effects of the pharmaceutical and vaccine compositions (Brunsvik [*actually Fredriksen (Examiner's correction)*] (2007); Schjetne (2007); Fredriksen (2006)).

Examiner's Reply

The Examiner appreciates the detailed explanation, the copies of the reference articles, and the technical effort into characterizing a single vaccibody embodiment, namely, that for generating an anti-idiotypic response against the monoclonal antibody-producing murine MOPC315.4 multiple myeloma in the mouse model in vivo in the specification, and the addition studies for Id vaccines described in the references.

Applicants have established the credibility of the murine MOPC315.4 multiple myeloma mouse model;

Applicants have established with the Id Vaccibody, that a prophylatic and therapeutic effect could be generated against the mouse MOPC315.4 tumor in vivo to block tumor progression by generating an anti-idiotypic response with the VH/VL idiotype of the Vaccibody.

Schjetne (2007) establishes that a clonotypic CD40-expressing tumor in mice could be targeted with Ig-like vaccine construct directed against CD40;

Fredriksen (2006) appears to be the publication of the data presented in the instant specification; and

Fredriksen (2007) establishes that a clonotypic tumor in mice (B lymphoma (A20)) or MOPC315) could be targeted with an Ig-like vaccine construct targeting MIP-1alpha and RANTES.

Notably and significantly, Applicants have not shown that the similar results for generating an anti-idiotype response that was both therapeutic and prophylactic could be generated against for example a human xenograft of multiple myeloma or lymphoma cells in an animal model. Further, Applicants have not shown that the myriad combinations of antigenic units and targeting units for a single monomeric unit encompassed by the claims have actually been used in a construct, administered to an animal model bearing any relevant disease much less multiple myeloma or lymphoma in order to generate a) both a T-cell and B-cell immune response, b) an immunologically

effective response against MM or lymphoma, where the response was therapeutic and/or preventative.

The examiner submits that one of ordinary skill in the art could not reasonably make the correlation or prediction that from a single animal model using a single clonotypic tumor with a single Vaccibody, that any Vaccibody embodiment could be used in vivo to treat or prevent any disease much less multiple myeloma in any animal including a human. Applicants' entire presentation does not provide sufficient enablement to practice the scope of the inventive claims.

Examiner draws Applicants attention to the critically important work of Voskoglou-Nomikos (Clin. Can. Res. 9:4227-4239 (2003)). Voskoglou-Nomikos conducted a study using the Medline and Cancerlit databases as source material in comparing the clinical predictive value of three pre-clinical laboratory cancer models: the in vitro human cell line (Figure 1); the mouse allograft model; and the human xenograft model (Figures 2 and 3). Significantly when each of the cancer models was analyzed against Phase II activity, there was a negative correlation for the in vitro human cell line models being predictive of good clinical value. No significant correlations between preclinical and clinical activity were observed for any of the relationships examined for the murine allograft model. And the human xenograft model showed good tumor-specific predictive value for NSCLC and ovarian cancers when panels of xenografts were used, but failed to predict clinical performance for breast and colon cancers. Voskoglou-Nomikos suggests that "the existing cancer models and parameters of activity in both the preclinical and clinical settings may have to be

redesigned to fit the mode of action of novel cytostatic, antimetastatic, antiangiogenisis or immune-response modulating agents" and "New endpoints of preclinical activity are contemplated such as the demonstration that a new molecule truly hits the intended molecular target" (p.4237, Col. 1, ¶6).

Dennis (Nature 442:739-741 (2006)) also recognizes that human cancer xenograft mouse models for testing new drugs has been and will remain the industry standard or model of choice, but it is not without problems because "many more [drugs] that show positive results in mice have little or no effect in humans" (p. 740, Col. 1, ¶3). Dennis describes transgenic animal mouse models as an alternative to xenograft modeling and the general differences between mice and humans when it comes to tumor modeling: 1) cancers tend to form in different types of tissue, 2) tumors have fewer chromosomal abnormalities, 3) ends of chromosomes (telomeres) are longer, 4) telomere repairing enzyme active in cells, 5) short lifespan, 6) fewer cell divisions (10^{11}) during life than humans (10^{16}), 7) metabolic rate seven time higher than humans, and 8) lab mice are highly inbred and genetically similar. One skilled in the art would reasonably conclude that evidence obtained in mouse xenograft models would not even necessarily correlate with results expected in human multiple myeloma or lymphoma.

For all of the foregoing reasons, this aspect of the rejection is maintained.

b) Applicants' allegations on pp. 24-25 of the Response of 1/22/08 have been considered and are found persuasive.

Applicants' admission on the record is that the "dimmers" ["dimers"] in the present application are formed from homodimers, which assemble spontaneously from

the expression products of one single vector (due to the presence of the dimerization unit in the monomers). It should be noted that only expression of one vector is necessary in order for the claimed embodiments to work."

New Grounds for Objection

Claim Objections

18. Claim 83 is objected to for reciting in the second "wherein" clause "said monomer unit each" (duplicate occurrence). The claim could more clearly be read as "each of said monomer unit".

19. Claims 96 and 98 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims are interpreted as both being drawn to the nucleic acid where said targeting unit have the ability to target a chemokine receptor. It is noted that the term "a" does not precede "chemokine receptor" in Claim 96. Nevertheless, the scope of the claims is considered the same.

New Grounds for Rejection

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

20. Claims 83, 88-92, 95, 96, 98-100 and 118-126 are rejected under 35 U.S.C. 101 because Claims 83, 88-92, 95, 96, 98-100 and 118-126 are directed to a nucleic acid. The claims read on a nucleic acid that is found in nature. Products of nature do not constitute patentable subject matter as defined in 35 USC 101. See MPEP 2105. Since a nucleic acid encoding a monomer unit does not exist in nature in purified form, it is suggested that Applicant use the language "isolated" or "purified" in connection with the nucleic acid to identify a product that is not found in nature.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

21. Claims 83, 88-92, 95, 96, 98-100 and 118-126 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 83, 88-92, 95, 96, 98-100 and 118-126 are indefinite for the recitation "said monomer unit each comprises an antigenic unit and a targeting unit for an antigen

presenting cell" in Claim 83, because it is not clear if the antigenic unit or the targeting unit or both would be recognized by the APC.

b) Claim 100 is indefinite for the recitation “wherein said antigenic scFv is identical to a monoclonal Ig produced by myeloma or lymphoma" because one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of myeloma or lymphoma as presently claimed because each of the cells secretes or produces a full length monoclonal antibody (see specification at [0004]). It is not clear how the cells could naturally produce a recombinant antibody fragment identical to the scFv or how the scFv could identical to the monoclonal Ig unless the cells themselves were engineered to produce a monoclonal recombinant scFv. If Applicants are referring to the VH and VL domains for the scFv being derived from a monoclonal Ig, then amending the claim to introduce a description of this sort could overcome the rejection.

c) Claim 118 recites the limitation "said recombinant antibody-based molecule". There is insufficient antecedent basis for this limitation in the claim or in Claim 83.

Alternatively, the claim is indefinite because Claim 83 is drawn to a monomer unit of a recombinant antibody-based dimeric molecule. Thus it is not clear if the formulated nucleic acid of Claim 118 would express the monomer encoded by the nucleic acid or is formulated to express two monomer units in order to produce the recombinant antibody-based dimeric molecule.

Conclusion

22. No claims are allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn Bristol/
Examiner, Art Unit 1643
Temporary Signatory Authority